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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,709	02/24/2005	Hirokazu Kubota	Q86272	7656

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EXAMINER

MORRIS, PATRICIA L

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/525,709

Applicant(s)

KUBOTA ET AL.

Examiner

Patricia L. Morris

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Claims 1-7 are under consideration in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Betageri et al. (US 6,506,747) and Kubota et al. (US 6,958,339) in view of Haleblian et al. (J of Pharmaceutical Sciences, (1969), 58, pp 911-929), Chemical & Engineering News, Feb. 2003, Brittain et al. (Polymorphism in Pharmaceutical Solids, pages 1-2, 185), US Pharmacopia, 1995, pp 1843-1844, Muzaffar et al. (J. of Pharmacy (Lahore) 1979, 1(1), 59-66), Jain et al. (Indian Drugs, 1986, 23 (6), Taday et al. (J of Pharm. Sci, 92 (4), April 2003, 831-838) and Concise Encyclopedia Chemistry, page 872-873 (1993).

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Betageri et al. and Kubota et al. generically teach the crystal forms of the instant compound and as well as the pharmaceutical compositions. Note the compounds of formula I of Betageri et al. wherein R₄ represents pyridyl substituted by alkyl. Also, note compound no. 543 of Betageri et al. or example 36 Kubota et al. The specific reference differ only in not having applicants' methyl groups on the pyridyl ring. However, the references teach the art recognized equivalence of hydrogen and alkyl on the pyridyl ring. Haleblian et al., Muzaffar et al., Jain et al., Brittain et al. and Taday et al. teach that compounds exist as polymorphs. Chemical & Engineering News, Muzaffar et al., US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

Changing the form, purity or other physical characteristic of an old product does not render the new form patentable where the difference in form, purity or characteristic is inherent or rendered obvious by the prior art. In re Cofer 148 USPQ 268. Mere difference in physical property is a well known conventional variation for the same pure substance (see Brittain, p. 1-2) is *prima facie* obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is a lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form claimed. Processing a compound into a pharmaceutical composition could create a different polymorph than the polymorphs being claims or even back to the compound itself. See pages 912-913 of Habeblian or page 33 of Wall et al. Jain et al., pages 322-326 teach that manufacturing processes affect polymorphs. Taday et al. on page 831, teach “..Once in the desired crystalline form, the polymorphic state may be changed by incorrect storage or even during tablet preparation”. Doelker et al. Abstract, “One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or dosage form.” The specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. The X-ray diffraction and Infrared spectrum data in the specification only pertains to the compounds rather than the compositions being claimed.

Chemical & Engineering News discloses that formulation of drugs or pharmaceuticals in its metastable forms, for example, one polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. The specification lacks description of how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Disclosure of X-ray diffraction patterns for pharmaceutical

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compositions comprising the polymorphic forms are lacking in the specification. The X-ray diffraction patterns in figure 1 only supports the polymorphic forms of the compounds and not the pharmaceutical compositions. Jain et al., p 322-326, recite the manufacturing processes that affect polymorphs. Otsuka et al. On page 852 states « in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process”.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouché, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention

The nature of the invention is the preparation of novel polymorphic forms of the instant compound and compositions.

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State of the Prior Art

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Additionally, solids may form solvates. Polymorphs tend to convert from less stable to more stable forms. (See Chemical Engineering News, page 32). No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best work with the most stable polymorph, because it will not convert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News. Page 33, which will change the pharmacological effects of the drug. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

The amount of direction or guidance and the presence or absence of working examples

Figure 1 of the specification only discloses the X-ray diffraction pattern and infrared spectra of compounds of particular forms rather than the compositions being claimed in terms of the specific X-ray diffraction patterns. Polymorphs often change into other polymorphs during drug manufacture (See Chemical Engineering News) into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the pharmaceutical compositions. Further, in the aqueous phase, all physical forms

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are amorphous (see Ulicky). Also, note page 316 of Jain et al. where it is stated "when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"

Further, the specification has also not described how all the crystalline forms and composition being claimed will be maintained and prevented from converting to other forms when used in the treatment of inflammation. It is well recognized in the art that the compound is given to the subject in a physiological environment, *i.e.*, administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical form and biological activity results from the particular form instead of the solution state of the compound.

The breadth of the claims

The breadth of the claims are drawn to the specific polymorph forms and in addition to the pharmaceutical compositions.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,958,339 in view of Halebain et al., Brittain et al., Chemical & Engineering News, Muzaffar et al., Jain et al., Taday et al. and Concise Encyclopedia Chemistry.

339' generically embraces the instant compound and composition. The ancillary references that compounds are known to exist in different polymorphic forms. Hence, patentable distinction is not seen.

Drawings

The formal drawings filed on February 24, 2005 have been accepted.

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Conclusion

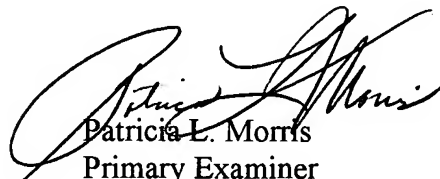
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688.

The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Patricia L. Morris
Primary Examiner
Art Unit 1625

plm
September 26, 2006